Setting the Stage: The Structure and Function of Neurons

The changes in behavior seen soon after consumption of alcohol—the acute effects of alcohol collectively referred to as intoxication—include impaired coordination of movements; errors in judgment about movements, distances, and time; impaired learning and memory; and sedation. Drinking moderate amounts of alcohol can produce a general depressant effect on behavior, whereas intake of large amounts of alcohol can lead to loss of consciousness and even coma or death from respiratory failure. These effects—as well as the euphoria and anxiety reduction seen with alcohol—all result from alcohol's actions on the brain.

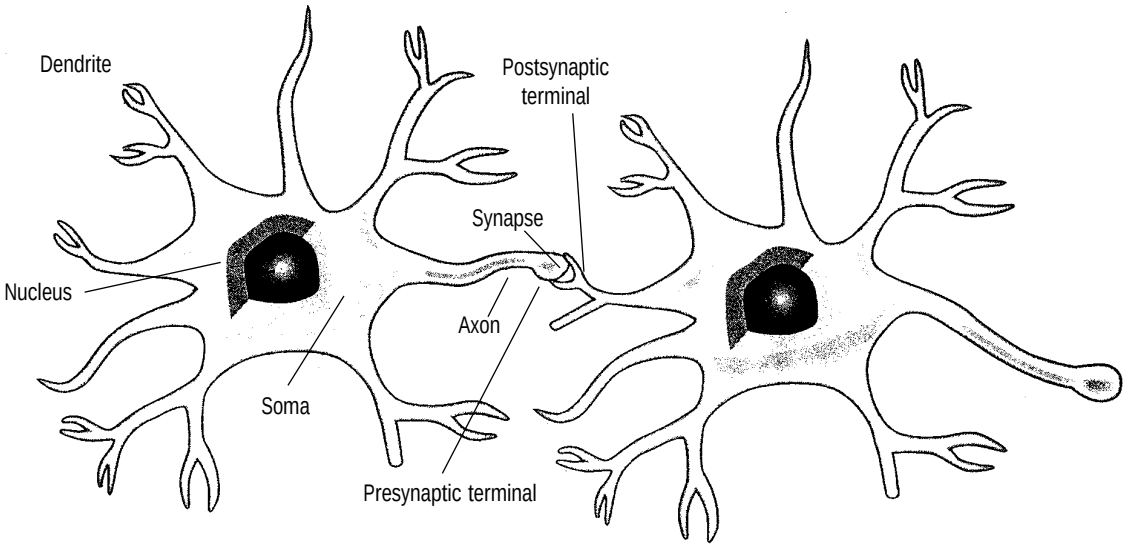
Exposure of the brain to alcohol initiates a process of adaptation that works to counteract the altered brain function resulting from initial exposure to alcohol. This adaptation or change in brain function is responsible for the processes called alcohol tolerance, alcohol dependence, and the alcohol withdrawal syndrome. Tolerance describes the process by which the brain becomes resistant to the effects of alcohol that lead to intoxication. This process results in a decrease in the amount of intoxication with time after alcohol drinking or after repeated alcohol drinking sessions, even when the amount of alcohol in the brain is the same as that which would originally have produced intoxication. For example, a level of brain alcohol that would produce movement problems minutes after beginning drinking will not produce the same severe intoxication hours after drinking was initiated. Further, in an individual who drinks heavily and often, the amount of intoxication produced by a particular level of alcohol in the brain is less than that in an individual who is drinking for the first time. These progressive changes in the behavioral effects of alcohol result when the brain becomes tolerant to its presence.

Prolonged exposure to alcohol can also cause the brain to become dependent on the presence of alcohol. Individuals who have been drinking steadily for long periods of time need to continue drinking to maintain an appropriate level of brain activity. These individuals will often report a strong desire, or craving, for alcohol and will become anxious and restless if deprived of alcohol for any significant period of time. Alcohol-dependent individuals will consume alcohol when given the opportunity, almost without regard to the social or environmental context. Laboratory animals also can exhibit signs of alcohol dependence that are manifest as heavy drinking whenever alcohol is available. Changes in the brain with long-term alcohol exposure appear to be the cause of alcohol dependence.

Cessation of drinking following long-term drinking will result in the development of a withdrawal syndrome. In the case of alcohol, withdrawal symptoms range from agitation and intense anxiety to tremors, full-blown seizures, and delusions. This withdrawal syndrome is another consequence of the adaptive changes the brain undergoes to continue functioning despite the presence of alcohol. As withdrawal progresses, the brain becomes free from the influence of the alcohol and its activity becomes markedly abnormal, with undesirable consequences for the mental, emotional, and behavioral status of the individual undergoing withdrawal.

Prolonged alcohol abuse will also result in the loss of brain nerve cells, or neurons. This effect appears to result from the direct toxic effects of alcohol and its metabolites in combination with the secondary consequences of the poor nutritional status of alcohol abusers and the neuronal damage that occurs during withdrawal (Charness 1993; Tsai et al. 1995). The section "The

Figure 1: Structural features of a presynaptic and postsynaptic neuron



Nerve cells called neurons contain different compartments that have distinct functions. The treelike dendrites receive chemical signals from other neurons and transmit electrical signals called synaptic potentials to the soma. The soma adds up these electrical signals from the dendrites, and if they are sufficiently large, it produces an electrical signal called the action potential that is conducted to the end of the cablelike axon. At the end of the axon is the axon terminal. This small, knob-shaped structure contains the neurotransmitter molecules that are released when the action potential reaches the axon terminal. These molecules act on other cells, and this is the basis for communication within the brain. The soma is also the site of the nucleus, which is responsible for controlling gene expression.

Source: Charness 1990.

Neurotoxicity of Alcohol" later in this chapter discusses neuronal loss and its consequences.

As will become clear in this and the accompanying sections in this chapter, alcohol alters the function of the brain by changing communication within and between neurons, the ultimate result being changes in brain activity and behavior.

Structure and Function of Neurons

Neurons are cells that are specialized to receive and rapidly conduct chemical and electrical signals. They have a distinctive shape with several appendages, or processes, extending from a rounded center (figure 1). Most neurons in the brain and spinal cord contain specific cellular compartments. Dendrites are treelike appendages that spread out in several directions from the rounded center of the cell; they are specialized to receive information from other cells. Chemicals released from other neurons interact with dendrites to initiate electrical impulses that can travel the length of the dendrite to the center of the neuron.

The neuronal center, or soma, contains the nucleus. The nucleus houses the cell's genetic material, deoxyribonucleic acid (DNA), which contains the information needed to synthesize the different proteins that the cell uses to function. Proteins are manufactured within the neuronal soma by a two-stage process (see the box "From DNA to Protein: How Genetic Information Is Realized"). The specific sequence of the nucleotide base molecules in the DNA within the nucleus gives rise to a unique sequence of the nucleotides in the corresponding messenger ribonucleic acid (mRNA). This process of RNA synthesis, called transcription, takes place within the neuronal nucleus. The RNA is then transported outside of the nucleus, to the ribosomes, where the amino acid building-block molecules of proteins are assembled in an order based on the sequence of nucleotide molecules in the RNA. This process is called translation. After the protein is synthesized, it can be moved to the appropriate part of the neuron to perform its given function.

From DNA to Protein: How Genetic Information Is Realized

All the genetic information necessary to create and maintain an organism is encoded in long, threadlike deoxyribonucleic acid (DNA) molecules in the nucleus of each of the organism's cells. But how is this information converted into the proteins that compose a significant portion of the cell's components and drive most chemical reactions in the body? This conversion, called gene expression, is a complex biochemical process that consists of several steps occurring in the cell nucleus and in the cytoplasm. To better understand how gene expression works, it helps to review briefly the chemical structure of DNA. The characteristic design of DNA molecules is the basis for the reactions involved in gene expression.

The building blocks of DNA, the nucleotides, are sugar molecules linked to organic bases. DNA includes four different organic bases: adenine (represented by the letter A), cytosine (C), guanine (G), and thymine (T). The order in which they are arranged specifies which amino acids will be linked to form a protein. Because more than four amino acids exist and are necessary to produce a protein, a triplet of three nucleotides represents (that is, codes for) one specific amino acid in the final protein. For example, the nucleotide triplet ATG codes for the amino acid methionine, and the triplet TGG codes for the amino acid tryptophan. The section of a DNA molecule containing the information needed to make one specific protein is called a gene.

DNA is a double-stranded molecule: two chains of nucleotides face each other and are connected through specific bonds. Because of the nature of these bonds, each nucleotide can bind to only one other particular nucleotide. For example, the nucleotide containing A always pairs with the nucleotide containing T, and the nucleotide containing C always pairs with the nucleotide containing G. The composition of the second strand therefore depends on the composition of the first strand. Accordingly, the strands are called complementary. This also means that if the nucleotide sequence of one strand is known, the sequence of the second strand can automatically be inferred.

Transcription

To convert the information encoded in the DNA of one gene into a protein, the first step is to copy, or transcribe, one of the DNA strands into another nucleic acid molecule called messenger ribonucleic acid (mRNA). This process is performed by specific enzymes in the cell nucleus.

There are different kinds of RNA in the cell that have different functions but the same chemical structure. RNA molecules are similar in their chemical composition to DNA molecules. The main differences are that the sugar component differs between DNA and RNA and that the organic base T present in DNA is replaced by the base uracil (U) in RNA. In addition, RNA molecules are single stranded; unlike DNA, they do not have a complementary strand.

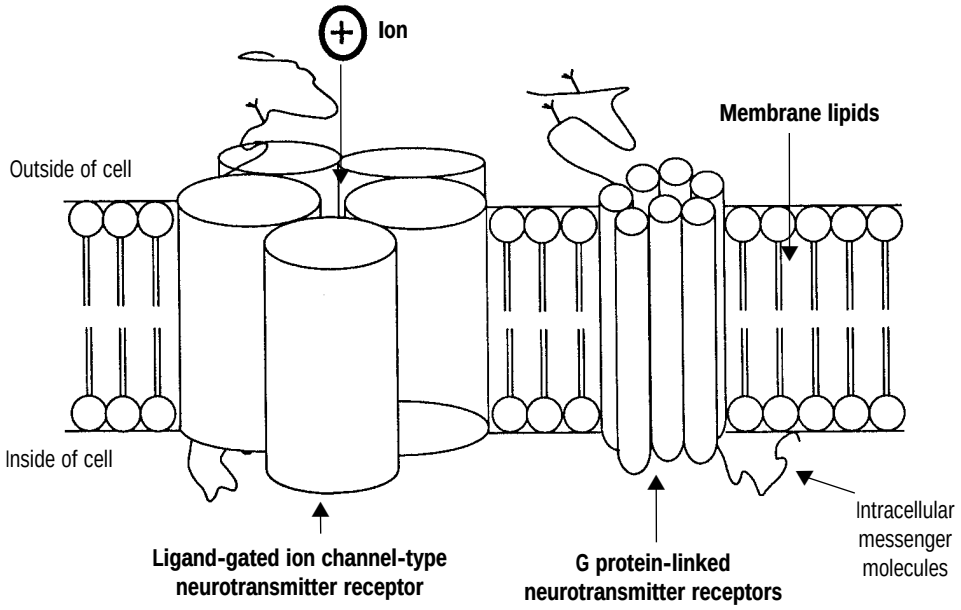
During transcription, the DNA sequence representing one gene is converted into mRNA. Only one strand of the double-stranded DNA molecule, however, serves as a template for mRNA synthesis; RNA nucleotides are guided to the DNA sequence that is being transcribed and temporarily bind to it. Again, only one specific RNA nucleotide can bind to each DNA nucleotide (for example, the RNA nucleotide containing A pairs with the DNA nucleotide containing T, and the RNA nucleotide containing C pairs with the DNA nucleotide containing G). This specificity guarantees that the genetic information contained in the DNA is accurately converted into mRNA. As with the DNA template, the sequence of a triplet of nucleotides in the RNA codes for one amino acid in the final protein.

After all the information for one gene has been copied into an mRNA molecule, the DNA and mRNA molecules separate. The mRNA then undergoes some additional modifications in the cell's nucleus before it is transported to the cytoplasm for the next step, the translation into the protein product.

Translation

In the cell's cytoplasm, macromolecules called ribosomes attach to, and slide along, the mRNA. In this manner, the ribosomes "read" the sequence of the mRNA's nucleotide triplets. According to that sequence, the ribosomes recruit a second kind of RNA, transfer RNA (tRNA), which guide the amino acids needed for protein synthesis to the mRNA-ribosome complex. One end of each tRNA molecule has a region that recognizes one specific nucleotide triplet on the mRNA. Another region of each tRNA molecule is attached to a specific amino acid. Thus, by recruiting tRNA molecules that recognize the nucleotide sequence of the mRNA, the ribosomes also retain the right amino acids in the right order to form the protein encoded by the gene represented in the mRNA. Specific enzymes then connect the amino acids until the complete protein is synthesized. Because each mRNA molecule can be read consecutively by several ribosomes, many protein molecules can be derived from just one mRNA template.

Figure 2: The lipid bilayer, including neurotransmitter receptors



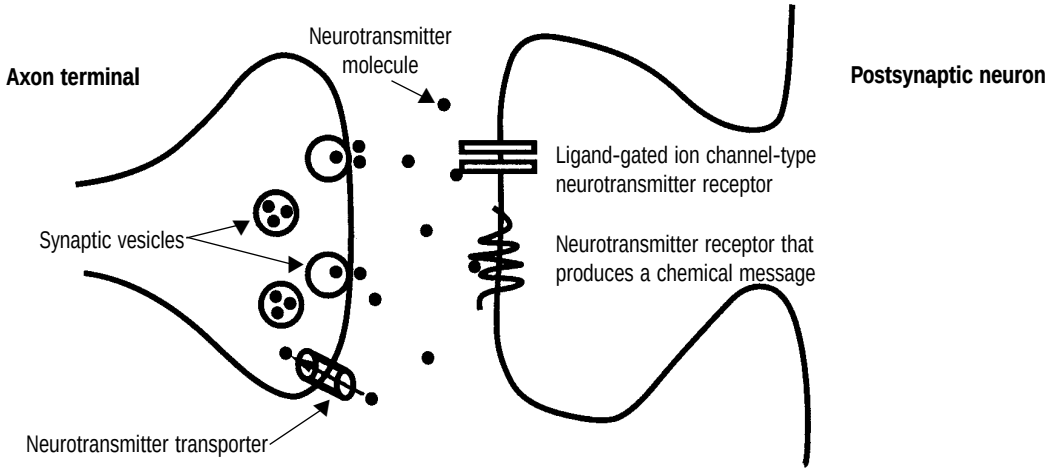
The cell membrane consist of two rows, or a bilayer, of lipid molecules with proteins inserted into the membrane. Two types of proteins that serve as receptors for brain neurotransmitters are depicted. Binding of neurotransmitters to G protein receptors leads to the binding and breakdown of guanosine triphosphate (GTP) and, in some cases, to the production of small-molecular-weight molecules known as second messengers.

In addition to housing the cell's genetic code, the soma is where electrical impulses from different dendrites mix. A single appendage known as the axon extends from the cell body; the end of the axon is called the axon terminal. Axons are specialized for carrying electrical signals arising from the soma. Unlike dendrites, axons and axon terminals are specialized for sending information from one nerve cell to the next. Nerve cells usually have only one axon, in contrast to the multiple dendrites that are found on each neuron.

The boundaries of all animal cells, including neurons, are defined by a membrane, known as the lipid bilayer, that consists of a double layer of fatty lipid molecules (figure 2). The purposes of this bilayer membrane are to separate the inside of the cell (intracellular environment) from the environment outside the cell (extracellular environment) and to separate one cell from another. This bilayer allows each cell to act independently of neighboring cells but still receive chemical and electrical information from other cells and from the extracellular environment.

Embedded within the lipids in the membrane are a variety of specialized proteins, many of which serve to communicate to the cell information coming from the extracellular environment or from other cells. Proteins in one class serve as channels through which ions (electrically charged atoms, in this case) can pass through the membrane from outside the cell to the inside of the neuron. Ion channel proteins are often classified according to how they are opened. Those that open in response to changes in the electrical charge, or potential, of the cell membrane are known as voltage-gated ion channels. Other ion channels bind to specific molecules in the extracellular environment and open the channel; these are ligand-gated ion channels (see figure 2). The movement of ions

Figure 3: Synaptic transmission



Schematic representation of a synapse between two neurons in the brain. The presynaptic axon terminal contains neurotransmitter molecules packaged in synaptic vesicles that are released into the synaptic cleft. The neurotransmitter molecules in the synaptic cleft bind to neurotransmitter receptors that reside in the membrane of the dendrite of a postsynaptic neuron. Removal of a neurotransmitter from the synaptic cleft is performed by neurotransmitter transporters that return the neurotransmitter to the inside of the neuron.

through these channel proteins produces electrical signals in the cell. The normal operation of both voltage-gated and ligand-gated ion channels is critical for maintaining proper neuronal signaling.

Communication Within and Between Neurons

Electrical signals help fulfill the neuron's major role—to communicate information quickly so that the brain can carry out its many functions. Transmission of information by nerve cells is accomplished through the opening of ion channels along the entire length of the neuron. When impulses from different dendrites mix and produce an electrical signal that exceeds a certain voltage threshold, a summed electrical signal originating in the soma is created. The cell fires in response to the summed electrical signal in an all-or-none manner: no new signal is triggered if the threshold is not reached, but if the threshold is reached, the electrical impulse or action potential that is conducted down the axon arrives at the axon terminal essentially unaltered relative to its size at the soma.

At the axon terminal, the action potential initiates a sequence of biochemical events that leads to the release of a neurotransmitter into the synapse, the gap between two neurons positioned close together (figure 3). The neurotransmitter—a chemical messenger of which there are many types in the brain—then acts on the next cell. Through this process, the axon terminal turns the electrical signal in the neuron into a chemical signal that allows for transmission of information in the brain.

The presynaptic side of the synapse, the axon terminal, is specially designed to release neurotransmitters. Neurotransmitters are stored in small membrane-bounded packets, called vesicles, inside the axon terminal. When the action potential reaches the axon terminal, it triggers the combining of the membrane of the vesicle with the membrane of the cell in a process called vesicle fusion. The molecular events linking the action potential to vesicle fusion depend on the presence of calcium ions. The fused vesicle opens and releases its neurotransmitters into the synaptic cleft between the two neurons.

Although several types of neurotransmitters are found throughout the brain and spinal cord, only one or two types of neurotransmitters are released at any given synapse.

After the neurotransmitter is released from its vesicle, it crosses the synaptic cleft. The neurotransmitter then acts on the second, or postsynaptic, neuron. The actions of the neurotransmitter on the postsynaptic neuron begin with the neurotransmitter interacting with, or binding to, specialized proteins called neurotransmitter receptors on the dendrites of the postsynaptic neuron.

Synaptic transmission is tightly controlled by the regulation of the amount of time that the neurotransmitter stays in the synaptic cleft after each instance of transmitter release. Specialized proteins called neurotransmitter transporters regulate neurotransmitter levels in the synaptic cleft. These transporter molecules sit on the membranes of the presynaptic, and sometimes the postsynaptic, neurons facing the synaptic cleft. When neurotransmitter levels in the synaptic cleft are high, the transporter molecules take up the neurotransmitters and return them to the presynaptic terminal, where they are recycled to be used in a new round of synaptic transmission. Changes in the activity of neurotransmitter transporters allow neurotransmitters to remain in the synaptic cleft longer than usual and will thus lengthen the duration of synaptic transmission.

Binding of a particular neurotransmitter molecule released into the synapse by one neuron to its specific receptor on the dendrites of the adjacent neuron produces either an electrical or a chemical signal within the second neuron. The electrical signals are produced by receptors that contain ligand-gated ion channels. Binding of the neurotransmitter ligand to the receptor serves to open the molecular gate of the ligand-gated ion channels.

The types of ions that pass through the membrane's ion protein channels determine the response of the neuron. Neurons become activated when the voltage across their membranes becomes more positive relative to the membrane's voltage at its resting state. At rest, neurons maintain a membrane potential of around –65 millivolts, which means that the interior of the neuron is negatively charged with respect to the fluid surrounding the cell. Entry of positively charged ions, or cations, tends to excite neurons, making them more likely to transmit information from one brain region to the next. Entry of negative ions, or anions, makes the voltage across the cell membrane more negative and discourages the transmission of information from one neuron to the next. Activation of ligand-gated ion channels produces very rapid responses in neurons. The electrical current produced when these receptors are activated occurs within thousandths of a second (milliseconds).

The proteins in the cell membrane that activate production of chemical messages within neurons are another form of neurotransmitter receptor (see figure 2). These receptors do not form ion channels, but instead interact with other proteins inside the cell to stimulate the formation of chemical messengers. Chemical messages within cells generally act more slowly than changes produced when ion channels are activated. Modification of proteins by intracellular messengers occurs over a time course of hundredths of seconds to minutes. Chemical messages to the nucleus can cause alterations in protein expression that can last for hours to days, producing long-lasting changes in the function of individual synapses and cells.

Binding of a neurotransmitter to one of these receptors activates enzymes that stimulate messenger formation in a process known as signal transduction. Through this process, cells receive information about the chemicals outside the cell and respond accordingly. The molecules formed immediately after activation of receptor proteins are called second messengers. (The neurotransmitter is the first messenger.) One of the most common second messengers is cyclic adenosine monophosphate (cAMP).

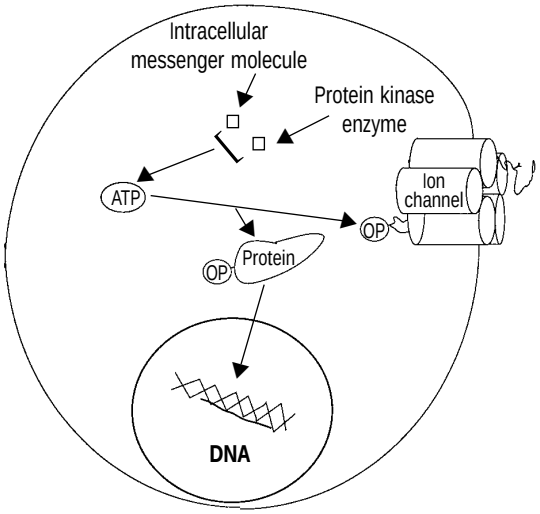
Second messengers can modify proteins by initiating a series of biochemical reactions that lead to the addition or removal of small molecules to or from the protein. This process is called posttranslational modification because it occurs after translation, the last step in the genetically directed synthesis of proteins in the cell. One molecule that is often added to modify proteins is phosphate, which contains phosphorus and oxygen atoms. This process—phosphorylation—is triggered when second messengers activate enzymes known as kinases. Phosphorylation can alter the structure, function, and location of proteins within cells, including ion channel proteins, receptors, and enzymes (figure 4).

Phosphorylation of the proteins that constitute ion channels, receptors, and enzymes is the major control mechanism that neurons use to regulate the activity of these proteins. For example, depending on the type of ion channel, phosphorylation of the channel protein can either shorten or lengthen the time the ion channel is open, thus regulating the flux of ions into the neuron. These changes in ion flux—and the type of ion the affected channels carry—can increase or decrease the excitability of neurons. Because phosphorylation dynamically regulates the activity of neuronal receptors and proteins, neurons also have enzymes (phosphatases) that remove these phosphate groups in order to reverse the effects of phosphorylation. The coordinated activity of both protein kinases and phosphatases ultimately determines the extent of protein phosphorylation of important neuronal proteins. Recent findings suggest that many of the acute and chronic effects of alcohol may be mediated by changes in the level of phosphorylation of key ion channels and receptors.

Second messengers also can trigger biochemical reactions that alter gene expression (the series of steps whereby information contained in DNA leads to the synthesis of proteins). In this case, the intracellular messenger molecule formed inside the cell modifies proteins that can enter the cell nucleus (see figure 4). Once in the nucleus, these specialized proteins interact with DNA and alter how the DNA sequence is "read," or transcribed. For example, a signal to the nucleus might lead to increased production of components of ion channels through the stimulation of the genes that encode for the ion channel protein. Once formed, the protein products encoded by these genes are shipped to different parts of the neuron to perform their functions.

Changes in the amount or structure of proteins normally produced by nerve cells can lead to long-lasting changes in neuronal function. The ability of neurons to respond to extracellular signals through the production of second messengers that can alter DNA expression is key to communication between neurons.

Figure 4: Protein phosphorylation in a cell



The functions of different types of proteins within a cell can be altered by addition of a phosphate molecule (OP) to the protein in a process called protein phosphorylation. Two examples are shown in this illustration. An intracellular messenger molecule interacts with a protein kinase enzyme to stimulate transfer of the phosphate molecule from adenosine triphosphate (ATP) to an ion channel protein residing in the cell membrane. Phosphorylation of this protein could change its function, promote retention of the protein within the membrane, or lead to removal of the protein. Proteins that have the potential to interact with deoxyribonucleic acid (DNA) in the cell nucleus can also be phosphorylated. Phosphorylation of such a protein in the cell cytoplasm, outside of the nucleus, can lead to "translocation" of the protein to the nucleus, where the protein is free to interact with DNA and alter gene expression.

Neurotransmitters

Neurotransmitters clearly shape the stimulation and inhibition of neuronal activity. Many chemicals act as neurotransmitters in the brain. A large number of these neurotransmitters are relatively small molecules, including the amino acids gamma-aminobutyric acid (GABA) and glutamate. Each different neurotransmitter interacts with receptors that are specialized for binding only that neurotransmitter. Thus, a large variety of neurotransmitter receptors exist in the brain. The many possible interactions between the different neurotransmitters and their receptors allow neurons in the brain to generate different responses when their synapses are activated.

GABA

GABA is called an inhibitory neurotransmitter because through interactions with its receptors, GABA affects neurons in a way that reduces their activity. Activating or enhancing the function of GABA receptors usually decreases activity in brain neurons and can decrease activity of the entire brain and body, as occurs in general anesthesia.

GABA influences neuronal activity by binding to and activating several classes of GABA receptors (denoted $GABA_A$, $GABA_B$, and $GABA_C$). The GABA receptor that appears to be most sensitive to alcohol is $GABA_A$. This receptor is a ligand-gated ion channel that is composed of multiple subunits referred to as the alpha (α), beta (β), gamma (γ), delta (δ), epsilon (ε), and rho (ρ) subunits. Each subunit family includes multiple members that differ slightly in their amino acid sequence. Structural analysis of these subunits reveals that each GABA subunit traverses the neuronal membrane four times via transmembrane (TM) domains (designated TMI through TMIV) that are composed of 20 to 25 uncharged or nonpolar amino acids.

$GABA_A$ receptors appear to be assembled into a pentameric (five-unit) structure in which the TMII domains of each subunit face each other to form a pore through which chloride ions flow. The pore is normally closed to prevent flux of chloride ions across the membrane in the absence of a neurotransmitter. Binding of the neurotransmitter GABA to regions of the receptor outside of the cell opens the pore. The subsequent flux of chloride ions (as many as 100 million per second) hyperpolarizes the neuron and makes it much less likely to fire an action potential and, thus, less likely to transmit information from one cell to the next. In this way, GABA is inhibitory.

Glutamate

Glutamate, on the other hand, generally acts as an excitatory neurotransmitter that increases the activity of brain neurons by producing a response that is electrically opposite to that of the inhibitory neurotransmitters. Glutamate binds to specific ligand-gated ion channels and depolarizes the postsynaptic neuronal membrane, making it more likely that the neuron will fire. In this way, these proteins are excitatory; strong activation of glutamate receptors can lead to hyperexcitability of the brain and body—seizures are one manifestation. Within discrete brain regions and in individual neurons, the balance between GABAergic (GABA-activating) and glutaminergic (glutamate-enhancing) synaptic transmission is often the major determinant of the level of activity. By controlling the activity of these excitatory and inhibitory neurons, the brain can rapidly and profoundly alter the excitability of neurons.

In Closing

Alcohol appears to affect the function of several neurotransmitters by altering the communication mechanism between neurons at the point when a neurotransmitter activates its receptor. A large body of evidence suggests that this effect of alcohol on synaptic transmission is the major change in the brain that gives rise to intoxication. The following sections describe in detail some recent findings that are helping scientists understand how alcohol affects brain function.

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